Diphtheria

Report Immediately

1) THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

Diphtheria is caused by toxin-producing varieties of *Corynebacterium diphtheriae*, a gram-positive, irregularly staining bacterium. Whether diphtheria bacteria produce toxin depends on whether they happen to be infected by a virus carrying the toxin gene. The four strains or biotypes of *C. diphtheriae* in order of their likelihood of producing toxin is: gravis, mitis, intermedius, and belfanti.

B. Clinical Description

Diphtheria has two forms—respiratory and cutaneous. Respiratory (nasal, pharyngeal, tonsillar, and laryngeal) diphtheria is typically caused by toxin-producing (toxigenic) strains of *C. diphtheriae*; cutaneous disease can be caused by either toxigenic or nontoxigenic strains. In the respiratory form of the disease, a membrane is formed; this membrane is usually visible on the throat or tonsils. Respiratory diphtheria begins 2 to 7 days after infection. Initial symptoms of illness include a sore throat and low-grade fever; swelling of the neck ("bull-neck") from inflammation can develop and is a sign of severe disease. Persons may die from asphyxiation when the membrane obstructs breathing. Other complications of respiratory diphtheria are caused by remote effects of the diphtheria toxin; these include myocarditis (inflammation of the heart) and nerve paralysis. Case fatality rates of 5–10% for respiratory diphtheria have changed little in 50 years. The respiratory form of diphtheria usually lasts several days; complications can persist for months.

Membranous pharyngitis from nontoxigenic *C. diphtheriae* is also reportable, although disease is usually mild and cannot cause systemic complications. The isolation of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. Although the frequency with which this occurs is unknown, a small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms. Rarely, other *Corynebacterium* species (*C. ulcerans* or *pseudotuberculosis*) may produce diphtheria toxin and lead to classic respiratory diphtheria. *Note:* Other pathogens can cause a membrane of the throat and tonsils, including *Streptococcus* species; Epstein-Barr virus and cytomegalovirus; *Candida*; and anaerobic organisms (Vincent's angina).

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains, is usually mild, typically consisting of nondistinctive sore or shallow ulcers and only rarely involving toxic complications (1–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

C. Reservoirs

Humans are the only host of *C. diphtheriae*.

D. Modes of Transmission

Diphtheria is transmitted person-to-person by droplet or direct contact with the nasopharyngeal secretions of an infected person. Contact with articles soiled with discharges from cutaneous lesions of infected people can be a source, but this has rarely been documented. Raw milk has served as a vehicle for transmission.

E. Incubation Period

The incubation period is usually 2 to7 days but may occasionally be longer.

F. Period of Communicability or Infectious Period

The infectious period typically lasts 2 to 6 weeks after infection. If patients are treated with antibiotics, communicability usually lasts less than 4 days. However, chronic carriage may occur, even after antimicrobial

therapy. Patients are considered infectious until two successive pairs of nose and throat cultures (and cultures of skin lesions in cutaneous diphtheria) obtained ≥ 2 weeks after completion of antimicrobial therapy and ≥ 24 hours apart are negative. (See Section 4) B. 2. d [page 4] for more details.) Asymptomatic carriers are important in sustaining transmission.

G. Epidemiology

Infection can occur in immunized, partially immunized and unimmunized persons. However, it is usually less severe in those who are partially or fully immunized. Diphtheria is endemic in many parts of the world, including countries of the Caribbean and Latin America. The incidence of respiratory diphtheria is greatest in the fall and winter, but summer epidemics may occur in warm moist climates in which skin infections are prevalent. During the last few years, large epidemics of diphtheria, primarily in adolescents and adults, have occurred in the former Soviet Union, Algeria, and Ecuador. In the states of the former Soviet Union (including Russia, the Ukraine and Central Asian Republics), over 150,000 cases and 5,000 deaths due to diphtheria occurred between 1990 and 1997. In recent epidemics in the former Soviet Union, the case fatality ratio has ranged from 3% to 23%.

While most cases of diphtheria reported recently in the United States were related to importation, enhanced surveillance in a previously endemic area (a Northern Plains Indian community) has revealed ongoing circulation of a toxigenic strain of *C. diphtheriae* first identified in that region in the 1970s. The last known case in Massachusetts occurred in 1994 in an unvaccinated 4-year-old child; this was a fatal case, and the source could not be identified. It is estimated that more than 40% of US adults lack protective levels of circulating antitoxin.

2) REPORTING CRITERIA AND LABORATORY TESTING SERVICES

A. What to Report to the Massachusetts Department of Public Health

- A suspect or confirmed case of diphtheria. Laboratory confirmation includes isolation of *C. diphtheriae* from a clinical specimen, or histopathologic diagnosis of diphtheria.

Note: See Section 3) below for information on how to report a case.

B. Laboratory Testing Services Available

Bacteriological **culture** and **toxigenicity testing** of the resulting isolate are essential for confirming diphtheria. Both of these procedures are available at the Massachusetts State Laboratory Institute (SLI). Clinical specimens for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. Except in situations where the index of suspicion is low, close contacts should be cultured as well.

Attachment A (at the end of this chapter) describes the procedures for collecting specimens for culture and subsequent toxigenicity testing. Attachment B (at the end of this chapter) gives an overview of the diagnostic tests that may be useful in confirming infection, which include **PCR** and **serologic testing**, available at the Centers for Disease Control and Prevention (CDC).

3) DISEASE REPORTING AND CASE INVESTIGATION

A. Purpose of Surveillance and Reporting

- To alert public health authorities to the circulation of *C. diphtheriae* and the possibility of other cases developing in the area, particularly given the large number of susceptible adults.
- To assure early and appropriate treatment with diphtheria antitoxin and antibiotics.
- To obtain necessary laboratory specimens before antibiotic or antitoxin treatment.
- To identify and evaluate contacts and provide necessary antimicrobial prophylaxis to prevent further spread of the disease.

B. Laboratory and Healthcare Provider Reporting Requirements

Refer to the lists of reportable diseases (at the end of this manual's Introduction) for specific information.

Note: Due to the potential severity of diphtheria, the Massachusetts Department of Public Health (MDPH) requests that information about any case be **immediately reported** to the local board of health where diagnosed. If this is not possible, call the MDPH Division of Epidemiology and Immunization at (617) 983-6800 (weekdays) or (617) 983-6200 (nights/weekends).

C. Local Board of Health Reporting and Follow-up Responsibilities

MDPH regulations (*105 CMR 300*) stipulate that each local board of health (LBOH) must report the occurrence of any case of diphtheria (as defined by the reporting criteria in Section 2A). Refer to the *Local Board of Health Reporting Timeline* (at the end of this manual's introductory section) for information on prioritization and timeliness requirements of reporting and case investigation.

Note: The MDPH requests that information about any suspect or known case of diphtheria be **immediately reported** to the MDPH Division of Epidemiology and Immunization by calling (617) 983-6800 (weekdays) or (617) 983-6200 (nights/weekends).

Note: Due to national surveillance and reporting requirements, the Massachusetts Immunization Program (MIP) takes the lead on diphtheria case investigation (including filling out the official case report form) and disease control recommendations, in collaboration with the local board of health. MIP will keep the local board of health informed of all significant developments and will request the assistance of the board of health as needed.

D. Initial Question to Ask Healthcare Provider and Patient

In order to assess the likelihood that a suspect case is a true case prior to laboratory testing, MIP and/or other public health staff helping in the investigation should ask about: 1) symptoms, 2) diphtheria immunization history, 3) recent history of travel (to where and dates), 4) whether there were any recent out-of-town visitors (from where and dates), and 5) whether there was any recent contact with anyone with similar symptoms.

4) CONTROLLING FURTHER SPREAD

This section provides detailed control guidelines that are an integral part of case investigation. LBOHs should familiarize themselves with the information. However, the Massachusetts Immunization Program will take the lead on implementing control measures, in collaboration with the board of health.

A. Isolation and Quarantine Requirements (*105 CMR 300.200*)

The Isolation and Quarantine Requirements (promulgated November 1998, printed July 1999) are out of date with respect to diphtheria. Current recommendations of CDC and MDPH (as of 2000) are as follows:

Minimum Period of Isolation of Patient

Maintain isolation until two successive pairs of nose and throat cultures (and cultures of skin lesions in cutaneous diphtheria) obtained $\geq$ 2 weeks after completion of antimicrobial therapy and $\geq$ 24 hours apart are negative. If there was no antimicrobial therapy, these two sequential pairs of cultures should be taken after symptoms resolve and $\geq$ 2 weeks after their onset. If an avirulent (nontoxigenic) strain is documented, isolation is not necessary.

Minimum Period of Quarantine of Contacts

Contacts whose occupations involve handling food must be excluded from that work until two successive pairs of nose and throat cultures obtained $\geq$ 2 weeks after completion of antimicrobial prophylaxis (if any) and $\geq$ 24 hours apart are negative. These requirements may be extended to other contacts who work in high-risk transmission settings, as determined by MDPH.

B. Protection of Contacts of a Case

Close contacts are defined as those who sleep in the same house or who share food, drink, or eating/drinking utensils with the case, as well as healthcare workers in contact with the case's oral or respiratory secretions.

Those contacts who were in brief contact with the case, but do not meet the definition for close contact are not considered significant contacts.

Below, management of cases and contacts is divided into four categories: 1) cases, 2) cases and symptomatic close contacts, 3) asymptomatic close contacts, and 4) nonsignificant contacts. It is important to follow the sequence of actions given, as administration of antibiotics, diphtheria antitoxin (DAT), and diphtheria toxoids will interfere with interpretation of diagnostic testing. Attachment C (at the end of this chapter) presents these recommendations in diagram form.

1. **Cases**
   Isolate the respiratory case on droplet precautions until two cultures from both the nose and the throat are negative for toxigenic *C. diphtheriae*. Place the cutaneous case on contact precautions until two cultures of skin lesions are negative. Material for all these cultures should be taken $\geq$ 2 weeks after cessation of antimicrobial therapy and $\geq$ 24 hours apart. If there was no antimicrobial therapy, the cultures should be taken after symptoms resolve, $\geq$ 2 weeks after their onset, and $\geq$ 24 hours apart. Continue as described in Section 2 immediately below.

2. **Cases and Symptomatic Close Contacts**
   a. Collect cultures as described in Attachment A (located at the end of this chapter). If antibiotics have been started, it is useful to collect specimens for PCR and serology as well, which are described in Attachment B (at the end of this chapter). Serology specimens should be collected *before* administration of DAT or diphtheria toxoid.
   b. After collection of specimens, cases and symptomatic close contacts should begin antibiotic treatment as follows:
      - erythromycin parenterally (40 to 50 mg/kg/day, maximum 2 g/day) until patient can swallow comfortably, at which point either oral erythromycin in 4 divided doses or oral penicillin V, 125–250 mg 4 times a day, may be substituted, for a total treatment period of 14 days; **or**
      - aqueous crystalline penicillin G intramuscularly (100,000 to 150, 000 U/kg/day, in four divided doses) for 14 days; **or**
      - aqueous procaine penicillin intramuscularly (25,000 to 50,000 U/kg/day, maximum 1.2 million U, in two divided doses for children and 1.2 million U for adults) for 14 days.
   c. Cases and symptomatic close contacts should also be evaluated for initiation of therapy with diphtheria antitoxin (DAT). DAT can be obtained through an Investigational New Drug (IND) protocol via CDC. Healthcare providers treating a case of suspect diphtheria can contact the diphtheria duty officer directly at the CDC Child Vaccine-Preventable Disease Branch, Epidemiology and Surveillance Division, National Immunization Program in Atlanta. (See Attachment D at the end of this chapter for important telephone numbers.) If serology specimens are to be collected, this should be done *before* administration of DAT.
   d. If cases or symptomatic close contacts are culture-positive, they will need two repeat pairs of nose and throat cultures taken $\geq$ 2 weeks after antibiotics have been discontinued and $\geq$ 24 hours apart. If a case or symptomatic close contact has not received antibiotics, two successive pairs of nose and throat cultures taken after symptoms resolve, $\geq$ 2 weeks after the onset of symptoms, and $\geq$ 24 hours apart are needed.
      - If both sets of cultures are negative, the individual is considered free of infection.
      - If any of the repeat cultures is positive, an additional 10-day course of oral erythromycin should be administered, and follow-up cultures will need to be repeated as described.
   e. Cases and symptomatic close contacts who are not up to date should be immunized with a diphtheria toxoid-containing preparation appropriate for age during convalescence. (Please refer to Sections 4) B. 3 and 4) C. below for recommendations on completing the schedule.) Remember, if serum is to be collected, do this before vaccinating.
   f. Close contacts should be monitored for symptoms daily for at least 7 days after their last exposure. Active surveillance for suspect cases in the affected settings should take place for at least two incubation periods (10 days).

3. **Asymptomatic Close Contacts**
   a. Where diphtheria is confirmed or highly suspected in the case, all asymptomatic close contacts should have cultures collected as described in Attachment A (at the end of this chapter).
   b. Assess and monitor for signs and symptoms of diphtheria for at least 7 days.
   c. Assess diphtheria toxoid vaccination status and vaccinate as outlined below:
      - If < 3 doses or unknown, administer a dose of diphtheria toxoid (DTaP, DT, or Td as appropriate) and complete primary series according to schedule.
      - If ≥ 3 doses and last dose was >5 years ago, administer a booster dose of diphtheria toxoid.
      - If ≥ 3 doses and last dose was < 5 years ago, children needing their fourth primary dose or booster dose should be vaccinated; otherwise vaccination is not required.

   All close contacts (regardless of their culture result or immunization status) should begin antibiotic prophylaxis with oral erythromycin (40–50 mg/kg/day for 7 days, maximum 2 g/day, for children; and 1/g/day for adults. A single IM dose of benzathine penicillin G (600,000 U for persons < 6 years of age and 1,200,000 U for persons ≥ 6 years of age) is an alternative. (The lower dose of penicillin is for patients weighing less than 30 kg.)
   d. All asymptomatic close contacts who were initially culture-positive will need two repeat pairs of nose and throat cultures taken ≥ 2 weeks after antibiotics have been discontinued and ≥ 24 hours apart. If an asymptomatic contact has not received antibiotics, two successive pairs of nose and throat cultures taken ≥ 24 hours apart are needed. If any of the repeat cultures is positive, an additional 10-day course of oral erythromycin should be given and the cultures repeated as described above.
   e. Close contacts should be monitored for symptoms daily for at least 7 days after their last exposure. Active surveillance for suspect cases in the affected settings should take place for at least two incubation periods (10 days).

4. **Non-Significant Contacts**
   Contacts who do not sleep in the same house as the case; do not share food, drink, or eating/drinking utensils with the case; and are not healthcare workers in contact with the case's oral or respiratory secretions should be immunized with the appropriate diphtheria toxoid-containing preparation as described in Section 4) B. 2. e) above. They do not need to be cultured or placed on antibiotic prophylaxis.

C. Preventive Measures

Personal Preventive Measures/Education

Vaccination, including routine childhood vaccination and Td boosters beginning at age 11–12 years and continuing every 10 years thereafter, is the best preventive measure against diphtheria. Tetanus toxoid-containing formulations should always be used. The Advisory Committee on Immunization Practices (ACIP) recommends that all children receive a routine series of five doses of tetanus- and diphtheria-containing vaccine at ages 2, 4, 6, 15–18 months, and 4–6 years. Booster doses of diphtheria and tetanus toxoids should then be administered beginning at age 11–12 years (provided at least 5 years have passed since the last dose) and every 10 years thereafter. DTaP and DT should be used in persons < 7 years of age, whereas Td is the preferred preparation for persons ≥ 7 years of age.

The Td catch-up schedule for those starting immunization at ≥ 7 years of age consists of 3 doses. The second dose is usually given 1–2 months after the 1st dose and the 3rd dose 6 months after the 2nd dose.

Due to the epidemiology of diphtheria worldwide, it is important for all international travelers to be up to date with respect to DTaP/DT/Td vaccination. Good personal hygiene (which consists of proper hand washing, disposal of used tissues, not sharing eating utensils, etc.) is also important in prevention.

Please refer to the most current versions of MDPH's *Immunization Guidelines* and *Massachusetts Immunization Program-Supplied Vaccines and Patient Eligibility Criteria* for details about DTaP/DT/Td vaccination, the recommended schedule, who should and shouldn't get the vaccine, and who is eligible to receive state-supplied vaccine. These as well as other relevant resources are available through the Division of Epidemiology and Immunization at (617) 983-6800 or (888) 658-2850. For more information regarding

international travel and diptheria, contact the CDC's Traveler's Health Office at (877) 394-8747 or through the internet at <http://www.cdc.gov/travel>.

ADDITIONAL INFORMATION

The following is the formal CDC surveillance case definition for diphtheria. It is provided for your information only. (CDC case definitions are used by the state health department and CDC to maintain uniform standards for national reporting.) For reporting to the MDPH, always use the criteria in Section 2A of this chapter.

Case Definition for Diphtheria (as defined by CDC, 1999)
Clinical Description
An upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory Criteria for Diagnosis
- Isolation of *Corynebacterium diphtheriae* from a clinical specimen, or histopathologic diagnosis of diphtheria.

Case Classification
Probable: a clinically compatible case that is not laboratory-confirmed and is not epidemiologically linked to a laboratory-confirmed case.
Confirmed: a clinically compatible case that is either laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case.

Comment
Cutaneous diphtheria should not be reported. Respiratory disease caused by non-toxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheria isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC.

REFERENCES

American Academy of Pediatrics. *Red Book 2000: Report of the Committee on Infectious Diseases, 25th Edition*. Illinois, Academy of Pediatrics, 2000.

CDC. Case Definitions for Infectious Conditions Under Public Health Surveillance. *MMWR*. 1997; 46:RR-10.

CDC. *Epidemiology & Prevention of Vaccine-Preventable Diseases: The Pink Book, 6th Edition*. CDC, January 2000.

CDC. *Manual for the Surveillance of Vaccine-Preventable Diseases*. CDC, 1999.

Chin, J., ed. *Control of Communicable Diseases Manual, 17th Edition*. Washington, DC, American Public Health Association, 2000.

MDPH. *Regulation 105 CMR 300.000: Reportable Diseases and Isolation and Quarantine Requirements.* MDPH, Promulgated November 1998 (Printed July 1999).

Attachment A: Collection of Specimens for Isolation of *C. diphtheriae* (1 page)
Attachment B: Overview of Requirements for Laboratory Testing for Diphtheria (1 page)
Attachment C: Algorithm for Diagnosis, Treatment, and Follow-Up of Suspect Diphtheria Cases and Infected Contacts (1 page)
Attachment D: Important Telephone Contacts for Diphtheria Control (1 page)

Note: These attachments are separate PDF files. To access them, go back to the *Guide to Surveillance and Reporting* main page, click on the D–G drop down menu, and each attachment is listed under Diphtheria.